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CHANGES IN PLASMA CORTICOSTERONE AND CATECHOLAMINE CONTENTS INDUCED BY LOW DOSES OF DELTAMETHRIN IN RATS*

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SUMMARY

The effects of low doses of (*S*)- α -cyano-3-phenoxybenzyl (1*R*)-cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylate (Roussel UCLAF, Paris, France), (deltamethrin) upon sympathetic-adrenomedullary and pituitary-adrenocortical activity were investigated in rats by measuring plasma noradrenaline (NA), adrenaline (A) and corticosterone (CS) concentrations. Blood was sampled from freely-moving animals provided with heart catheters at short intervals up to 60 min after intravenous administration of deltamethrin (0.05, 0.15 and 0.45 mg/kg) or vehicle. Behavioral activity was recorded shortly after the sampling times. Time course and magnitude of the biochemical changes were compared with the effects of exposure to uncontrollable white noise in a similar sampling and recording procedure.

Dose-dependent increases were observed for NA and A as well as for CS contents. The dose-response relations however, were different among the neuro-endocrine respondents. Discrete step-wise increases were observed for plasma CS only, indicating greater sensitivity for neurotoxic actions. Already at a dose of 0.15 mg/kg of deltamethrin, CS contents rose to values that were considerably higher than those found during noise exposure. In contrast, plasma CA concentrations increased to noise stress values only after the 0.45 mg/kg dose. The behavioral activity pattern appeared to resemble both CA patterns.

The results suggest that rather low doses of deltamethrin elicit vigorous autonomic and neuro-endocrine responses that indicate high levels of stress, presumably caused by the neurotoxic effect of the insecticide.

Key words: Deltamethrin, Plasma Catecholamines, Plasma Corticosterone, Insecticides, Rats.

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INTRODUCTION

Pyrethroids are widely used neurotoxic insecticides which may have detrimental effects on behavioral, autonomic and neuro-endocrine functions of mammals, including man. High doses of the pyrethroid deltamethrin (1.5 and 2.6 mg/kg i.v.) that induce severe behavioral disturbances (tremors, writhing spasms) in rats have been shown to result in extremely high plasma noradrenaline (NA) and adrenaline (A) concentrations [1]. Plasma NA and A contents reflect the degree of neuro-sympathetic and adrenomedullary activity [2,3], and a relationship has been found between the magnitude of plasma catecholamine (CA) changes and the degree of behavioral activation and anxiety induced by environmental stressors [4,5]. The purpose of the present study was to assess whether plasma CA changes could serve as biochemical indices of neurotoxic effects of low doses of deltamethrin that induce less severe or no overt behavioral disturbances. In addition, the impact on the release of another stress-related hormone, corticosterone (CS) (reflecting pituitary-adrenocortical activity), was determined, in order to compare the relative sensitivities of neuro-endocrine adaptation systems for detecting neurotoxic properties of chemicals. Moreover, time-course and magnitude of the deltamethrin induced biochemical changes were compared with the effects of exposure to an environmental stressor (noise stimulation).

MATERIALS AND METHODS

Male Wistar rats (300–350 g) were housed individually in clear plexiglass cages (25 × 25 × 30 cm) with free access to food and water under conditions of constant temperature ($21 \pm 2^\circ\text{C}$) and a fixed 12-h light/12-h dark photoperiod (lights on from 0800 to 2000 h).

Under ether anesthesia, animals were provided with a silicon cannula (i.d., 0.5 mm; o.d., 1.0 mm) into the entrance of the right atrium via a jugular venotomy. This method allows frequent blood sampling during several hours without disturbing the animal [6,7]. For at least 1 week animals were allowed to recover from surgery and to habituate to the sampling procedure.

Between 1000 and 1200 h on the day of the experiment, 0.35-ml blood samples were taken under baseline conditions at –10 and 0 min and at short intervals up to 60 min after the start of i.v. administration of deltamethrin (0.05, 0.15 and 0.45 mg/kg) or vehicle (glycerol/formal). After each blood sample an equal volume of transfusion blood was given. All 8 animals used were sampled under all 4 doses, using a balanced repeated measures within-subject design with an inter-test interval of 1 week. Behavior was rated by the experimenter just before, during and shortly after each blood sampling. Behavioral activity was qualitatively classified into the following categories: (0) resting: lying down in a stretched or curled up-like position; (1) alert: slow moving through the cage, sniffing; (2) active: eating, drinking, grooming, scratching; (3) excited: fast locomotor activity, burrowing and pawing.

In a separate experiment, 7 animals were tested before, during and after

exposure to uncontrollable white noise (10 min, 100 dB) in a similar sampling and recording procedure.

Blood samples were collected in chilled (0°C) centrifuge tubes containing heparin as anti-coagulant. For the determination of plasma CA, an aliquot of 200 µl blood was immediately pipetted into chilled tubes containing EDTA and reduced glutathione to prevent CA degradation. After centrifugation, supernatants were removed and stored at -30°C until assays were performed.

Plasma NA and A concentrations were determined in duplicate according to a radioenzymatic COMT-procedure described previously [8]. Plasma CS contents were measured in duplicate according to a competitive protein-binding method as described [9].

Values are presented as means \pm S.E.M. Responses were quantified by computing integrated areas above the baseline, i.e. area under the curve (AUC) for the response time-course. Analysis of variance for repeated measures (multivariate model where appropriate and possible; when not possible the conservative Greenhouse-Geisser correction for the numbers of degrees of freedom in the univariate test was applied [10]) and post-hoc paired *t*-tests were used for statistical evaluation.

RESULTS

The effects of acute intravenous deltamethrin administration on plasma CS, NA and A and on occurrence of behavioral symptoms are shown in Fig. 1 for all doses used. A 2-factor ANOVA on each parameter with dose as univariate (4 levels) and sampling time as multivariate (6 levels) within-subject factor was performed. For all parameters measured significant main effects of dose (CS: $F(3,21) = 4.69$, $P < 0.05$; A: $F(3,21) = 5.02$, $P < 0.01$; NA: $F(3,21) = 9.6$, $P < 0.001$; behavior: $F(3,21) = 58.5$, $P < 0.001$) and sampling time (CS: $F(5,3) = 19.38$, $P < 0.05$; A: $F(5,3) = 12.82$, $P < 0.05$; NA: $F(5,3) = 10.11$, $P < 0.05$; behavior: $F(5,3) = 58.5$, $P < 0.01$) were found. The interaction dose \times time, using the conservative Greenhouse-Geisser correction, was significant for CS ($F(1,7) = 9.44$, $P < 0.05$) and behavior ($F(1,7) = 14.78$, $P < 0.01$).

The AUC values for the measured parameters are shown in Fig. 2. Using a 2-factor ANOVA on the biochemical data with dose as univariate (4 levels) and hormonal variable as multivariate within-subject factor (3 levels) revealed, in addition to significant main effects of dose and hormonal variable, a significant multivariate interaction ($F(6,2) = 84.3$, $P < 0.05$) indicating different dose-response relations among the neuro-endocrine respondents. Post-hoc analysis revealed that at the doses tested discrete step-wise increases were observed for plasma CS only. Already after the lowest dose of deltamethrin a significant response was observed.

Significant behavioral changes were observed after dosing with 0.15 and 0.45 mg/kg. Striking effects on behavior were seen after the 0.45 mg/kg dose:

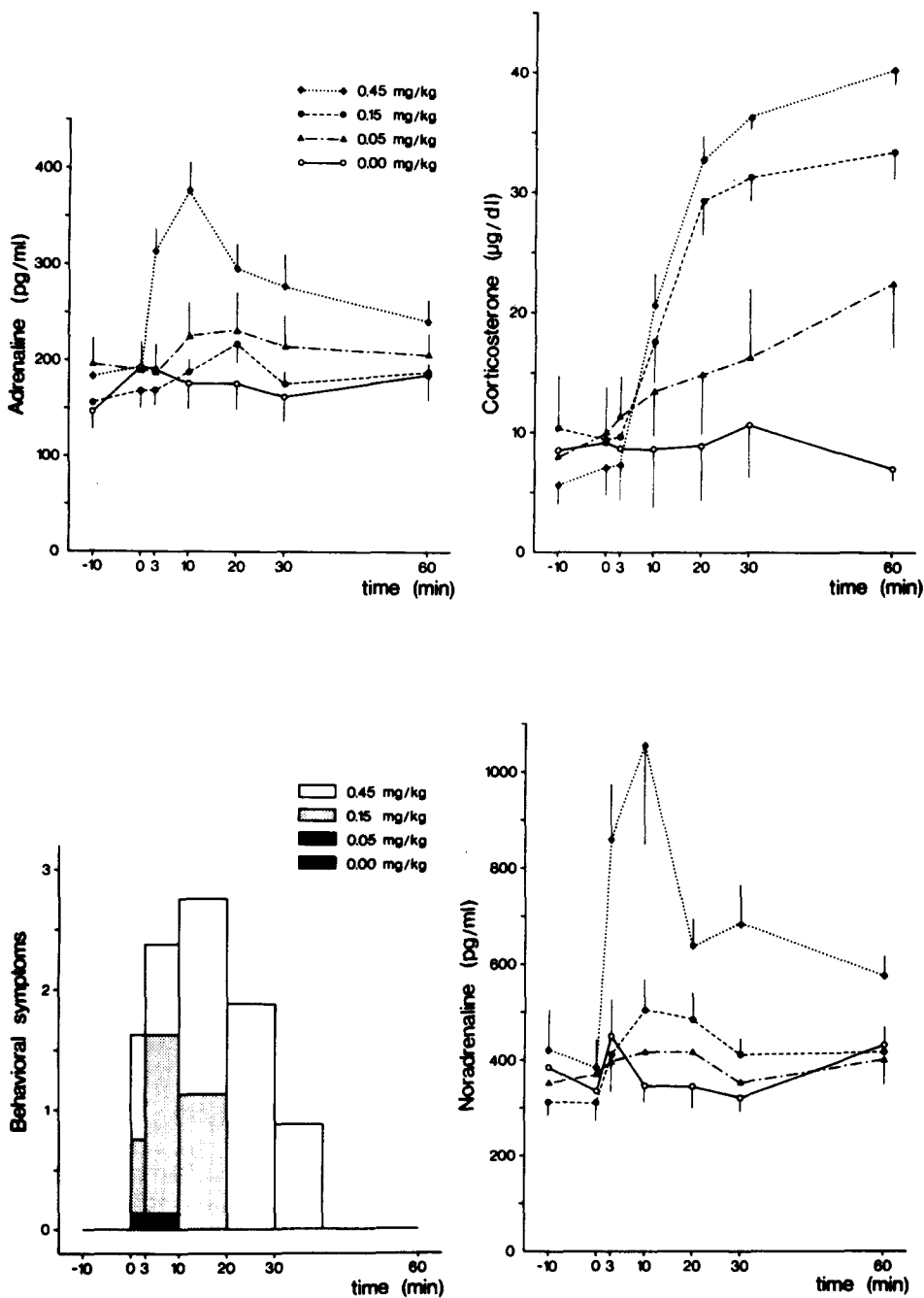


Fig. 1. The time-course effects of acute intravenous deltamethrin administration on plasma noradrenaline, adrenaline and corticosterone concentrations as well as on behavioral activity (vertical bars denote \pm S.E., $n = 8$).

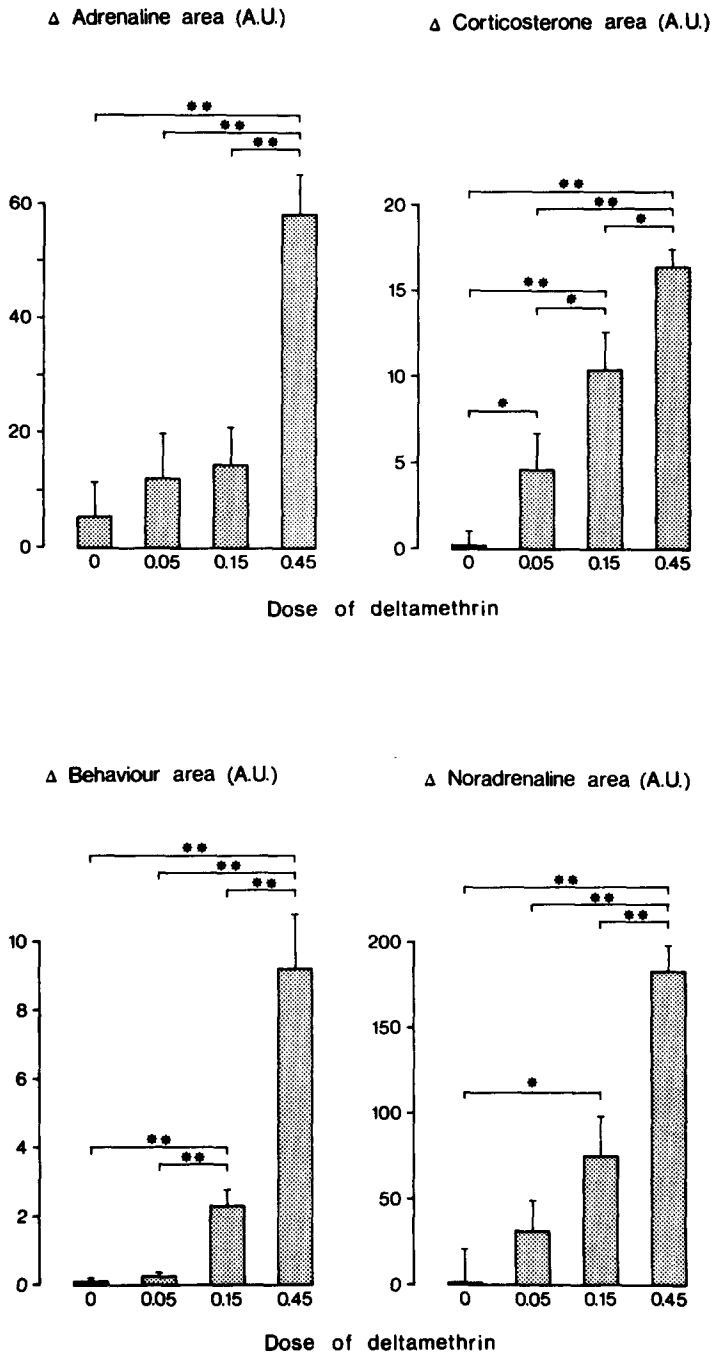


Fig. 2. Integrated responses of plasma noradrenaline, adrenaline and corticosterone as well as behavioral activity after i.v. dosing with 0, 0.05, 0.15 and 0.45 mg/kg deltamethrin. (Horizontal bars denote significant post-hoc comparisons among responses; * $P < 0.05$; ** $P < 0.01$).

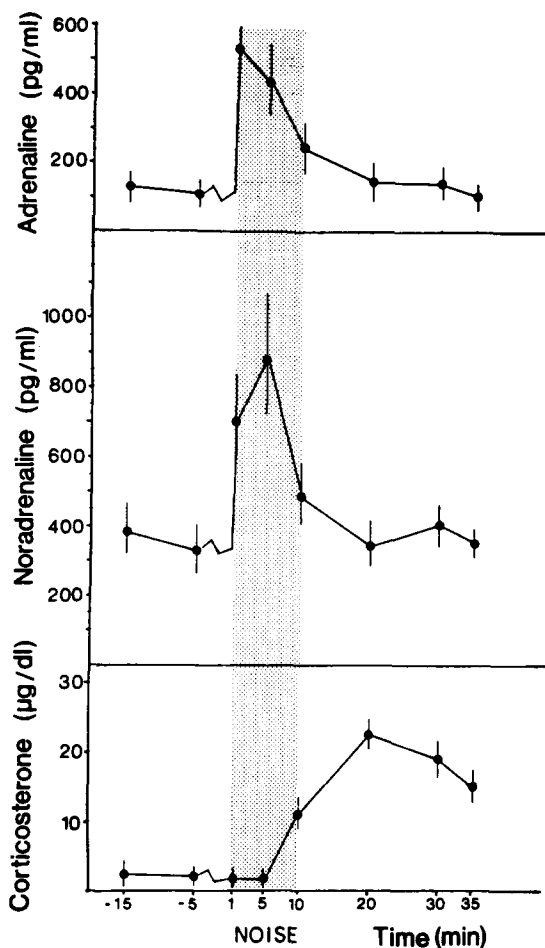


Fig. 3. Effects of 10 min white noise exposure (100 dB) on plasma noradrenaline, adrenaline and corticosterone concentrations. (Mean \pm S.E., $n = 7$).

the animals became very excited and were displaying pawing and burrowing episodes, lasting 20–30 min.

The effects of 10-min noise stimulation (100 dB) on plasma NA, A and CS concentrations are shown in Fig. 3. During noise stimulation plasma NA and A concentrations were significantly ($P < 0.05$) elevated, and were declining to baseline values after cessation of exposure. Plasma CS contents started to rise after 5 min of noise onset and were significantly increased compared to baseline after the 10 min of noise exposure.

DISCUSSION

The present study shows that NA, A and CS in plasma are markedly

increased after i.v. administration of deltamethrin and that the dose-response relations for the neuro-endocrine effects are different. Discrete step-wise increases were observed for CS only, and already after the low dose of 0.05 mg/kg deltamethrin a significant plasma CS response was seen, whereas no change in NA, A or behavioral activity occurred at that dose. This suggests that plasma CS concentrations, as index of pituitary-adrenocortical activity, might be a more sensitive biochemical index for the (neurotoxic) actions of deltamethrin than plasma NA and A contents, and also more sensitive than behavioral concomitants of neurotoxicity. The concentrations reached by CS after dosing with 0.15 and 0.45 mg/kg are considerably higher than those found after the psychological stress of noise exposure. High CS values of about 40 $\mu\text{g/dl}$ have been reported in rats subjected to intense physical stressors like ether exposure or formalin injection [11], and presumably represent almost maximal pituitary-adrenocortical stimulation.

Time-course and magnitude of the deltamethrin-induced changes were similar for NA and A. Also their dose-response relations were grossly the same, indicating that both the neural and adrenomedullary part of the sympathetic autonomic nervous system was similarly affected by the insecticide. At the highest dose of deltamethrin (0.45 mg/kg) the increases in plasma NA and A concentrations were similar to those found in rats subjected to noise stimulation. Since 0.45 mg/kg of deltamethrin induced behavioral symptoms of toxicity such as prolonged episodes of burrowing and pawing, the change in CA content may be interpreted as a sign of pathological disturbance in the autonomic nervous system. With higher doses extremely high plasma NA and A values of more than 10 ng/ml have been found by Cremer and Seville [1].

The similarity between the time pattern of overt behavioral reactions and CA profiles indicate a relationship between deltamethrin-induced behavioral activity and plasma CA. A correspondence between normal daily as well as stress-induced physical(muscle) activity and plasma CA has also been found by others [2,5,12–14]. A known mechanism of action of pyrethroids is a delay of closing sodium channels of excitable membranes, thereby altering the action potential-induced increase in cytosolic Ca^{2+} and thus influencing calcium-dependent neurohumoral release processes [15]. It has been shown that deltamethrin increases the secretion of noradrenaline after stimulation of the sympathetic nerve in isolated rabbit hearts [16]. Therefore, a direct deltamethrin-induced stimulation of peripheral sites of CA release might also be possible.

The data suggest that rather low doses of deltamethrin elicit vigorous autonomic and neuroendocrine responses that indicate high levels of stress, presumably caused by the neurotoxic property of the insecticide.

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